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Heterogeneity in head and neck IMRT target design and clinical practice

Theodore S. Hong^a, Wolfgang A. Tome^{b,c,d}, and Paul M. Harari^{b,*}

^aDepartment of Radiation Oncology, Massachusetts General Hospital Cancer Center, Boston, USA

^bDepartment of Human Oncology, University of Wisconsin, Madison, USA

^cDepartment of Medical Physics, University of Wisconsin, Madison, USA

^dDepartment of Biomedical Engineering, University of Wisconsin, Madison, USA

Abstract

Purpose—To assess patterns of H&N IMRT practice with particular emphasis on elective target delineation.

Materials and methods—Twenty institutions with established H&N IMRT expertise were solicited to design clinical target volumes for the identical H&N cancer case. To limit contouring variability, a primary tonsil GTV and ipsilateral level II node were pre-contoured. Participants were asked to accept this GTV, and contour their recommended CTV and PTV. Dose prescriptions, contouring time, and recommendations regarding chemotherapy were solicited.

Results—All 20 institutions responded. Remarkable heterogeneity in H&N IMRT design and practice was identified. Seventeen of 20 centers recommended treatment of bilateral necks whereas 3/20 recommended treatment of the ipsilateral neck only. The average CTV volume was 250 cm³ (range 37–676 cm³). Although there was high concordance in coverage of ipsilateral neck levels II and III, substantial variation was identified for levels I, V, and the contralateral neck. Average CTV expansion was 4.1 mm (range 0–15 mm). Eight of 20 centers recommended chemotherapy (cisplatin), whereas 12/20 recommended radiation alone. Responders prescribed on average 69 and 68 Gy to the tumor and metastatic node GTV, respectively. Average H&N target volume contouring time was 102.5 min (range 60–210 min).

Conclusion—This study identifies substantial heterogeneity in H&N IMRT target definition, prescription, neck treatment, and use of chemotherapy among practitioners with established H&N IMRT expertise. These data suggest that continued efforts to standardize and simplify the H&N IMRT process are desirable for the safe and effective global advancement of H&N IMRT practice.

Keywords

IMRT; Head and neck; Target design; CTV definition; Contouring

Intensity modulated radiation therapy (IMRT) affords opportunity to alter the spectrum and severity of toxicities experienced by head and neck (H&N) cancer patients [1]. The ability to

Conflict of interest statement

None of the authors has a conflict of interest regarding the work presented in this manuscript.

conform radiation dose distribution is particularly useful in the H&N region due to the tight proximity of gross disease and “at-risk” nodal regions to normal structures including salivary glands, spinal cord, auditory apparatus, optic apparatus, mandible, larynx and others.

Target definition for H&N IMRT is particularly complex and requires a detailed knowledge of H&N anatomy and pathways of tumor spread. Several guidelines have been proposed in an effort to help standardize the H&N target delineation process [2-7]. These guidelines translate surgically and radiographically defined neck nodal levels for the practicing radiation oncologist. Site-specific treatment recommendations regarding nodal station coverage are thus provided from historical surgical data and from patterns of locoregional failure.

The overall complexity of H&N target delineation, coupled with strong dependence on physics support and rigorous quality assurance, leaves open the possibility of considerable heterogeneity in IMRT practice across institutions. Additionally, optimal dose and fractionation schedules for H&N IMRT have not been uniformly adopted [8]. Indeed, general H&N cancer management issues, such as the use of chemotherapy or neck dissection, also remain ill-defined for the IMRT patient. This study was therefore undertaken to assess current international patterns of H&N IMRT practice with particular emphasis on elective target delineation.

Materials and methods

Following Institutional Review Board approval, 20 centers from the USA, Europe, Australia, and Asia were solicited to design H&N IMRT target volumes for the identical H&N cancer case (T2 N1 M0, Stage III squamous cell carcinoma of the tonsil). Seventeen academic institutions were selected based on established expertise in H&N IMRT including publication track record in H&N radiation oncology, and three private US centers were selected based on experience with community H&N IMRT practice. The participating physicians and institutions are listed in Appendix A.

All participants received a DICOM RT file containing the same anonymous H&N CT file with a pre-designated GTV contour file. A virtual “tumor” of the right tonsil measuring ~3 cm with a single 2 cm ipsilateral level II metastatic cervical node was pre-contoured on CT images to eliminate responder variability in GTV contouring (Fig. 1). No information regarding the HPV status of the patient was provided to study participants. Participating senior radiation oncologists were asked to accept this GTV, and contour their own conventional IMRT target volumes (i.e., CTV) and dose prescriptions. In addition, they were instructed to accept that level IV nodes would be treated using an anterior supraclavicular field to limit heterogeneous approaches to treatment of the low neck. The resulting contour sets were then returned to us for analysis. The target contours were analyzed for overall volume, treatment laterality, and nodal station coverage. We only assessed nodal station coverage and no attempt was made to determine how accurately these nodal stations had been outlined.

Individual dose and fractionation schemes were also analyzed. To compare varying fractionation schemes, equivalent dose in 2 Gy fractions (EQD_2) was calculated based on linear-quadratic formulation [9] as described below:

$$EQD_2 = \frac{nd \left(1 + \frac{d}{\alpha/\beta} \right) - \frac{\lambda}{\alpha} (T - T_k)}{\left(1 + \frac{2}{\alpha/\beta} \right)} \quad (1)$$

where n denotes the number of fractions, d the dose per fraction, nd the total dose, T the total time of treatment in days, T_k the kick-off time for accelerated repopulation, T_{eff} the effective tumor stem cell doubling time, and λ the proliferation rate $\lambda = \ln(2)/T_{\text{eff}}$. For these calculations we have employed the following parameters $\alpha/\beta = 10$ Gy, $\alpha = 0.35$ 1/Gy [9], the total treatment time, T , is calculated assuming a Monday treatment start and no breaks, $T_k = 28$ days [10], $T_{\text{eff}} = 3$ days [11].

Centers also completed a questionnaire regarding details of their overall H&N IMRT treatment approach, including recommendation for chemotherapy, overall target volumes, and total time spent contouring the requested head and neck target volumes. These responses were analyzed for means and standard deviations.

Results

All 20 of the solicited centers responded to the survey, yielding a response rate of 100%.

General H&N cancer management

Several differences in overall management for the sample H&N cancer patient were identified.

Ipsilateral vs. bilateral neck treatment

Of the 20 participants, 17/20 (85%) recommended treatment of bilateral necks whereas 3/20 (15%) recommended treatment of only the ipsilateral neck.

Chemotherapy

Eight of 20 participants (40%) recommended the use of chemotherapy for this sample case. The remaining 60% recommended treatment with radiation alone. The eight centers recommending systemic therapy all preferred cisplatin-based chemotherapy. Five participants specifically recommended a regimen of concurrent cisplatin 100 mg/m² delivered every 3 weeks during radiation.

IMRT management

Target coverage

Dose levels: Eight of the 20 centers recommended a single CTV dose level for elective target coverage. Twelve of 20 centers recommended two CTV dose levels (commonly designated “high risk CTV” and “low risk CTV”) and one center recommended three CTV dose levels. For five of the 12 centers using two CTV dose levels, the high risk CTV represented an expansion of the GTV that was treated to the same dose as the GTV.

Target volumes: Significant variations in elective target volume definition were found. The mean elective target volume irradiated across all 20 plans was 250 cm³. The standard deviation (SD) for volume irradiated was 136 cm³ and the overall range was 37–676 cm³. For plans in which a single elective CTV was used, the mean volume irradiated was 193 cm³ with a standard deviation of 99 cm³. For those using two CTV levels, the mean high-risk CTV volume was 82 cm³ with a standard deviation of 43 cm³ and the mean low-risk CTV volume was 205 cm³ with a standard deviation of 123 cm³.

Neck levels treated: Since participants were instructed to accept that level IV would be treated using a conventional anterior supraclavicular field, analysis of nodal levels was limited to levels I–III, V, and retropharyngeal (RP) nodes. These nodal station treatment results are summarized in Table 1. Analysis demonstrates consistent coverage of ipsilateral

levels IIa, IIb, and III. In addition, almost all centers (95%) covered the ipsilateral retropharyngeal (RP) nodes. The majority (85%) of centers elected to cover level Ib on the ipsilateral side. In contrast, greater heterogeneity was observed with regard to elective contralateral nodal coverage. Indeed, three of 20 centers recommended treatment of the ipsilateral neck only. Generally, contralateral neck levels IIa, IIb, and III were consistently covered. However, in contrast to ipsilateral coverage, fewer than half of centers elected to treat contralateral level Ib and RP nodes. Fig. 2 clearly shows the distinct approaches taken by different centers regarding elective nodal coverage.

Target expansion: The average recommended PTV expansion from the contoured CTV (to accommodate possible systematic and random errors) was 4.11 mm with a standard deviation of 3.19 mm and a range of 0–15 mm.

Dose and fractionation

Fractionation schedule: The 20 survey participants recommended 17 unique fractionation schedules. Table 2 lists the specific fractionation schedule recommended by each institution, as well as their preference regarding the use of chemotherapy. The Table 2 also provides tonsil GTV total dose, and EQD₂ calculations with and without proliferation for comparison. Fig. 3 shows an example of two distinct dose prescriptions corresponding to institutions 5 and 13 (cf. Table 2), illustrating the wide heterogeneity of target delineation and dose prescription characteristic of the overall study.

Total treatment time: The mean total treatment time (assuming Monday start and no treatment breaks) was 42 days $\pm$ 3.6 days.

GTV dose: The mean tonsil GTV dose was 68.7 Gy $\pm$ 2.1 Gy and the mean nodal GTV dose was 67.5 Gy $\pm$ 5.5 Gy. Only one institution did not treat the tonsil GTV and nodal GTV to the same dose as two different boost schemes (7 Gy $\times$ 3 HDR or 2 Gy $\times$ 12 IMRT) for the tonsil and removal of the neck node were recommended after treatment of the entire IMRT volume to 46 Gy. When EQD₂ values for each fractionation schedule were calculated for comparison (accounting for repopulation), the mean EQD₂ for the tonsil GTV was 61.3 Gy $\pm$ 1.79 Gy.

CTV dose: For the seven institutions that used a single CTV dose level, the mean CTV dose was 52.7 Gy $\pm$ 5.1 Gy. Of the remaining thirteen institutions that used two elective dose levels, the mean high-risk CTV dose was 63.5 Gy $\pm$ 5.0 Gy and the mean low risk CTV dose was 53.7 Gy $\pm$ 2.8 Gy.

Time contouring—The average time spent by participants in the H&N contouring process was 102.5 min $\pm$ 54.8 min. Participants further confirmed that they typically spent an average 143.8 min on actual H&N IMRT cases (SD = 75.2 min) in their own practice defining head and neck target and organ at risk volumes. Note that for the current survey case, a pre-defined GTV was provided to all participants thereby eliminating the need for GTV contour time.

Discussion

Intensity modulated radiation therapy in the management of H&N cancer affords the opportunity to deliver curative therapy with reduction in normal tissue toxicity. Clinical experience with H&N IMRT suggests equivalent locoregional control and survival rates to historical controls [12-18] with improvement in quality of life, particularly with regard to salivary function [19-24].

The overall management of H&N cancer patients is complex over and above IMRT-specific issues. The use of concurrent chemotherapy for advanced stage H&N cancer is now broadly embraced [25]; however radiation alone remains a standard approach for early stage patients [26]. In the current study, a challenging intermediate stage III tonsil case was presented, and there was divergence in recommendation regarding the use of chemotherapy. Forty percent of centers recommended the use of chemotherapy whereas 60% recommended treatment with radiation alone.

The issue of ipsilateral vs. bilateral neck treatment reflects further complexity in the management of H&N cancer patients. There is an established track record for ipsilateral radiation in early stage, well-lateralized tonsil cancer confirming low contralateral neck failure rates in well-selected patients (T1–2, well lateralized, no base of tongue or soft palate extension, N0–1) [27]. However, the most common global approach (pre IMRT era) has been bilateral treatment. The majority of centers in this study elected to treat bilateral necks with radiation for this T2 N1 M0 case. However, provision of more detailed aspects describing the primary tumor anatomy including presence or absence of tongue base and/or soft palate extension may have further influenced treatment recommendations in this case.

Intensity modulated radiation therapy does add considerable complexity to the management of H&N cancer patients. In particular, precise and standardized target definition has proved challenging. Historically, definitive H&N radiation has been delivered through opposed lateral shrinking field techniques, broadly covering tumor bed and at-risk nodal regions. Elective nodal coverage has been based on surgical data and patterns of recurrence studies, frequently employing a threshold risk value of 15–25% [28].

Although published guidelines exist to help standardize H&N target delineation, they do not appear to have gained universal adoption; even among established H&N IMRT experts as identified in this report. There may be several reasons for this variable adoption of published guidelines. First, H&N IMRT is still relatively new (5–10 years for most centers) and there is a clear learning curve that enables centers and individual practitioners to refine specific treatment methods with experience. Second, the guidelines themselves are complex, and require considerable study and subsequent correlation with three-dimensional H&N anatomy of the individual case under treatment. Third, the majority of guidelines published to date refer to the node negative (N0) H&N patient which offers a less complex challenge than the node-positive (N+) patient. Whereas there is but one N0 presentation, there exist a wide variety of N+ presentations depending on number, size, location, and regional infiltration of metastatic nodes. This feature creates a unique fingerprint for each H&N cancer patient that renders the application of simple anatomic guidelines a challenge. Fourth, technical differences in IMRT treatment and immobilization systems frequently prompt individual centers to adopt distinct practice patterns that influence target design and expansion. Fifth, H&N IMRT target design is time consuming with experienced H&N practitioners in this survey reporting 144 min on average for complete contouring of each case. The labor-intensive nature of this complex task may itself contribute to variations in practice across centers and individual practitioners. There are likely additional reasons for the variability observed in guideline adoption by H&N experts.

The practice of expanding CTV targets to PTV targets showed considerable variation in this study. In general, this expansion of CTV to PTV acknowledges systematic and random errors to ensure that adequate dose is delivered across the CTV. This study identifies a mean CTV to PTV expansion of 4.11 mm with a broad range of 0–15 mm. This range may reflect the variable confidence of individual centers regarding the capabilities of their particular IMRT system as well as perceived precision and daily reproducibility of their H&N immobilization techniques. In a study of set-up variations using conventional thermoplastic

H&N masking techniques, surprisingly large daily set-up errors were confirmed when 6 degrees of positional freedom were rigorously assessed throughout a complete H&N treatment course [29]. This degree of variation has prompted engagement of high precision image-guided techniques in an effort to diminish daily treatment set-up variations [30]. These technical system differences may influence the practice of CTV to PTV expansion by participating centers.

On first glance, the selection of a specific fractionation schedule appears almost institution-specific with 17 distinct schedules recommended by 20 centers for the identical tonsil cancer case. However, when these fractionation schedules are controlled for fraction size, overall treatment time, and repopulation, the resultant EQD₂ are quite similar across schedules. The proliferation corrected mean tonsil GTV EQD₂ is 61.3 Gy with a standard deviation of 1.8 Gy. This notable concordance in proliferation corrected EQD₂ may reflect the expertise of the participating centers with particular regard to H&N fractionation and overall treatment time. Nevertheless, EQD₂ calculations do not incorporate the effect of dose heterogeneity frequently observed in H&N IMRT.

The significant H&N IMRT practice heterogeneity (cf. Fig. 2) observed in this study occurred despite the fact that a fixed tumor GTV and nodal GTV was provided as a starting point for all participants. It is likely that additional practice heterogeneities may have emerged had these volumes not been pre-specified.

To assist a new generation of radiation oncologists that enter training each year in their mastery of H&N IMRT, continued efforts to provide rigorous educational opportunities are desirable. The H&N e-contouring sessions provided at ASTRO-sponsored meetings are exceptionally popular and reflect the strong need for H&N IMRT training by radiation oncology practitioners. However, the considerable variability in expert opinion showcased at these H&N e-contouring courses, and within this H&N IMRT survey, suggests there remains ample room to further advance and refine consensus guidelines and training modules for this challenging process. H&N cancer patients should be the ultimate beneficiaries of improved standardization of this highly complex and practitioner-dependent technical practice.

Conclusions

This study identifies significant heterogeneity in global patterns of practice for H&N IMRT, even among established H&N cancer experts. Considerable variation exists not only in H&N IMRT target definition and prescription, but also with regard to general H&N cancer management issues such as treatment of ipsilateral vs. bilateral necks and the use of concurrent chemotherapy. The variations in prescription are tempered by the high concordance of the equivalent dose in 2 Gy fractions (EQD₂) reflecting the dose/fractionation expertise of established H&N experts. However, the target definition and contour variations remain highly significant. This variation in practice technique presents notable challenges for comparative analysis of the existing literature, as well as for the incorporation of H&N IMRT into multi-institutional clinical trials. This study also confirms a substantial time investment by physicians in the target contouring process for each H&N cancer patient. Methods that further assist in education, standardization and simplification of the H&N IMRT process are desirable for the safe and effective global advancement of H&N IMRT practice.

Acknowledgments

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Appendix A

Senior radiation oncologist	Institution
Robert Amdur	University of Florida, Gainesville, FL
Jacques Bernier	Ospedale San Giovanni, Bellinzona, Switzerland
Jean Bourhis/Youngan Tao	Institut Gustave-Roussy, Villejuif, France
E. Brian Butler	Baylor College of Medicine, Houston, TX
June Corry	Peter MacCallum Cancer Institute, Melbourne, Australia
Pat Conway	Gunderson Clinic, La Crosse, WI
Avraham Eisbruch	University of Michigan, Ann Arbor, MI
Adam Garden	UT M.D. Anderson Cancer Center, Houston, TX
Cai Grau	Aarhus University Hospital, Aarhus, Denmark
Vincent Gregoire	UCL Clinique Univ. St. Luc, Brussels, Belgium
Paul Harari/Theodore Hong	University of Wisconsin, Madison, WI
Christopher Jones	Radiological Associates, Sacramento, CA
Quynh Le	Stanford University, Stanford, CA
Anne Lee	Pamela Youde Nethersole, Hong Kong, China
Nancy Lee	Memorial Sloan-Kettering Cancer Center, New York, NY
Peter Levendag	Erasmus/Daniel den Hoed Cancer Center, Rotterdam, Netherlands
Brian O'Sullivan/John Kim	Princess Margaret Hospital, Toronto, Canada
Jeanne Quivey	University of California, San Francisco, San Francisco, CA
Adam Raben	Christiana Care, Wilmington, DE
Rupert Schmidt-Ullrich	Virginia Commonwealth University, Richmond, VA

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Fig. 1. T2 N1 M0 sample tonsil cancer. Panels A and B depict representative CT images through the tonsil and nodal GTV respectively. Panel C shows lateral radiograph with tonsil GTV (red) and nodal GTV (green).

Fig. 2.
Heterogeneity in H&N target delineation. Nine distinct CTV designs which illustrate broad practitioner-dependent variation in target delineation strategies for the identical tonsil cancer case.

Fig. 3.
Dose prescription. Representative sample dose prescription from two different centers. See institutions 5 and 13 in Table 2 for specific fractionation schedule details.

Table 1

Summary of responder recommendations for target coverage of specific neck node levels.

Nodal level	Ipsilateral neck (% treating)	Contralateral neck (% treating)
Ia	10	10
Ib	85	15
IIa	100	80
IIb	100	60
III	100	80
V	65	20
RP	95	50

RP = retropharyngeal.

Table 2

The fractionation schedule for each institution with BED values calculated using linear quadratic formulation.

Institution	Fractionation schedule	Chemotherapy (y/n)	GTV absolute dose (Gy)	GTV EQD ₂ (without repopulation) (Gy)	GTV EQD ₂ (with repopulation) (Gy)
1	GTV 66 Gy [50 Gy (2 Gy × 25) + 16 Gy (1.6 Gy × 10 BID)]; CTV 50 Gy (2 Gy × 25)	N	66	65.5	58.8
2	GTV 67 (HDR bst) or 70 (EBRT bst) [46 Gy (2 Gy × 23) + 21 (7 Gy × 3) or 24 Gy (2 Gy × 12)]; CTV 46 Gy (2 Gy × 23) (ipsilateral post-RT neck dissection)	N	67 (HDR bst) or 70 (IMRT bst)	75.8 (HDR bst) or 70.0 (IMRT bst)	65.3 (HDR) or 59.6 (EBRT)
3	GTV 66 Gy (2 Gy × 33); CTV 50 Gy (2 Gy × 30) 6 days/week	N	66	66.0	62.7
4	GTV 70 Gy (2 Gy × 35); CTV 54 Gy (1.8 Gy × 30)	Y	70	70	59.6
5	GTV 69.96 Gy (2.12 Gy × 33); CTV 59.4 Gy (1.8 Gy × 33)	Y	70	70.7	61.3
6	GTV 69.96 Gy (2.12 Gy × 33); CTV 59.4 Gy (1.8 Gy × 33)	Y	70	70.7	61.3
7	GTV 70 Gy (2 Gy × 35); CTV 50 Gy (2 Gy × 25)	Y	70	70	59.6
8	GTV/Hi-risk CTV 72 Gy [54 Gy (1.8 Gy × 30) + 18 Gy (1.5 × 12) given pm treatment days 19–30 (BID)]; Lo-risk CTV 49.5 Gy (1.65 × 30)	N	72	70.7	63.8
9	GTV/Hi-risk CTV 70 Gy (2 Gy × 35) (6 days/week); Lo-risk CTV 50 Gy (2 Gy × 25) (6 days/week)	Y	70	70	62.8
10	GTV 66 Gy (2.2 Gy × 30); Hi-risk CTV 60 Gy (2 Gy × 30); Lo-risk CTV 54 Gy (1.8 Gy × 30)	N	66	67.1	60.5
11	GTV/Hi-risk CTV 66 Gy (2.2 Gy × 30); Lo-risk CTV 54 Gy (1.8 Gy × 30)	N	66	67.1	60.5
12	GTV 68.1 Gy (2.27 Gy × 30); Hi-risk CTV 60 Gy (2 Gy × 30); Lo-risk CTV 54 Gy (1.8 Gy × 30)	N	68.1	69.6	60.5
13	GTV 66 Gy (2.2 Gy × 30); Hi-risk CTV 60 (2 Gy × 30); Lo-risk CTV (1.8 Gy × 30)	N	66	67.1	60.5
14	GTV 69.3 Gy (2.1 Gy × 33); Hi-risk CTV 60 Gy (1.8 Gy × 33); Lo-risk CTV 54 Gy (1.63 Gy × 33)	N	69.3	69.8	60.5
15	GTV 66 Gy (2.2 Gy × 30); Hi-risk CTV 60 (2 Gy × 30); Lo-risk CTV 54 (1.8 Gy × 30)	Y	66	67.1	60.5
16	GTV/Hi-risk CTV 70 Gy [40 Gy (2 Gy × 20) + 30 Gy (1.5 Gy × 20 BID)]; Lo-risk CTV 55 Gy [40 Gy (2 Gy × 20) + 15 Gy (1.5 Gy × 10)]	N	70	68.8	62.2
17	GTV 72 Gy [36 Gy (1.8 Gy × 20) + 36 Gy (1.8 Gy × 20 BID)]; Hi-risk CTV 64 Gy [32 Gy (1.6 Gy × 20) + 32 Gy (1.6 Gy × 20 BID)]; Lo-risk 56 Gy [28 Gy (1.4 Gy × 20) + 28 Gy (1.4 Gy × 20 BID)]	N	72	70.8	64.2
18	GTV 70 Gy (2 Gy × 35); Hi-risk CTV 64 Gy (1.8 Gy × 35); Lo-risk CTV 60 Gy (1.7 Gy × 35)	N	70	70	59.6
19	GTV/Hi-risk CTV 67.4 Gy [36 Gy (1.8 Gy × 20) + 31.4 Gy (3.14 Gy × 10)]; Lo-risk CTV 54 Gy (1.8 × 30)	Y	67.4	69.8	63.3
20	GTV 70 Gy (2 Gy × 35); Hi-risk CTV 70 Gy (2 Gy × 35); Lo-risk CTV 50 Gy (2 Gy × 25)	Y	70	70	59.6
Average ± SD			68.7 ± 2.09	69.4 ± 2.22	61.3 ± 1.79